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A review of the Efficacy of 7.5% NaCl/6% Dextran-70 (HSD) in Experimental Animals and Humans

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Division of Military Trauma Research

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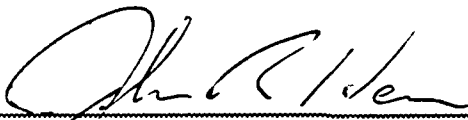
A Review of the Efficacy and Safety of 7.5% NaCl/6% Dextran-70 (HSD) in Experimental Animals and Humans, M.A. Dubick and C.E. Wade

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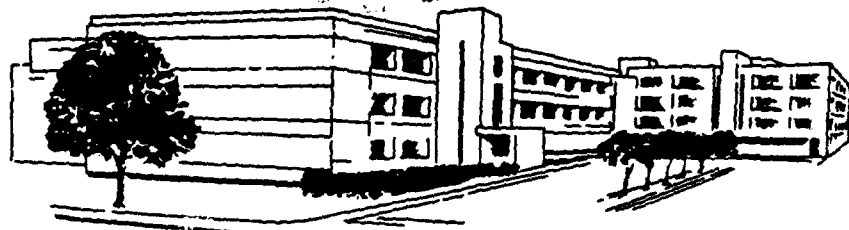
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Recent years have seen a renewed interest in the use of hypertonic-hyperoncotic solutions as plasma volume expanders for the treatment of hemorrhagic hypotension. In particular, a number of studies in experimental animals have addressed the efficacy and safety of small volume infusions of 7.5% NaCl/6% Dextran-70 (HSD). Employing models of fixed volume or fixed pressure hemorrhage, HSD has improved survival, and reversed many of the hemodynamic, hormonal, and metabolic abnormalities associated with hemorrhagic shock. In the few human field trials completed to date, HSD has been shown to be potentially beneficial in hypotensive trauma patients who require surgery or have concomitant head injury. Extensive toxicological evaluations and lack of reports of adverse effects in the human trials indicate that, at the proposed therapeutic dose of 4 ml/kg, HSD should present little risk.

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ABSTRACT

Recent years have seen a renewed interest in the use of hypertonic-hyperoncotic solutions as plasma volume expanders for the treatment of hemorrhagic hypotension. In particular, a number of studies in experimental animals have addressed the efficacy and safety of small volume infusions of 7.5% NaCl/6% Dextran-70 (HSD). Employing models of fixed volume or fixed pressure hemorrhage, HSD has improved survival, and reversed many of the hemodynamic, hormonal, and metabolic abnormalities associated with hemorrhagic shock. In the few human field trials completed to date, HSD has been shown to be potentially beneficial in hypotensive trauma patients who require surgery or have concomitant head injury. Extensive toxicological evaluations and lack of reports of adverse effects in the human trials indicate that, at the proposed therapeutic dose of 4 ml/kg, HSD should present little risk.

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A Review of the Efficacy and Safety of 7.5% NaCl/6% Dextran-70 (HSD) in Experimental Animals and Humans -- Dubick and Wade

The search for an ideal solution for effective resuscitation from hemorrhagic hypotension has stimulated much interest in both the civilian and military medical communities. In the civilian setting, this area of research has been predicated by the observation that the majority of the early deaths following trauma in the 60% of patients who survive to treatment is attributable to injuries resulting in severe blood loss (1). In general, these injuries are considered treatable if prompt, definitive care is administered. In addition, acute hemorrhage has long been recognized as the major cause of death in conventional warfare, accounting for about 50% of all fatalities (2). It has been predicted that in the military setting, early far-forward administration of first aid and resuscitation solutions could reduce mortality as much as 20% (2). Early far forward resuscitation of acute hemorrhage was also recognized as beneficial by British military medical personnel during the Falkland Islands War (Dr. Robert Mosebar, personal communication).

In the U.S. military, the concept of fluid resuscitation to treat hemorrhage was first reported during the Spanish-American War, when normal salt solution was given rectally or subcutaneously (3). During World War I it was believed that fluid therapy could be given orally or rectally, and intravenous (IV) administration of fluids was recognized as beneficial for severe cases of hemorrhage (3). The potential benefits of crystalloid solution for the treatment of shock or for situations requiring fluid replacement was well recognized by the beginning of World War II (3). Today, noncarbohydrate, nonprotein crystalloids such as Ringer's lactate (RL) are the preferred solutions for the treatment of hypovolemic shock (4).

Although the administration of large amounts of normal saline or balanced salt solutions for the treatment of hemorrhagic shock remains the current standard of care, it was recognized as early as 1937 that excess use of crystalloid solutions in shock states could be harmful (5). Consequently, over the

past 40 to 50 years, in an effort to determine their potential usefulness in the treatment of hypovolemic states, a large literature has developed exploring the physiological effects of both hypertonic salt solutions and hyperoncotic solutions.

A resurgence of research examining hypertonic resuscitation began with the study of Velasco, et al. (6) which showed that in an otherwise lethal hemorrhage model in dogs, infusion of 7.5% NaCl at 10% of the shed blood volume restored hemodynamic parameters and improved survival. This was subsequently confirmed by others (7,8).

The shortcoming of these solutions was the transient nature of the hemodynamic improvement they induced (9). Subsequently, 6% Dextran-70 was added as a colloid to induce a more prolonged cardiovascular response following resuscitation. This new solution, 7.5% NaCl/6% Dextran-70 or HSD was viewed as a major improvement in small volume resuscitation (9,10). Actually, dextrans themselves have a long history of use in the treatment of hypovolemia (11,12). In the 1940's and 1950's, more than 200,000 doses of dextran solutions were administered as a plasma volume expander (13), and in fact, the U.S. military used large doses of dextran solutions to resuscitate injured soldiers during the Korean War (3). As a plasma volume expander, HSD was a marked improvement over normal saline. HSD expanded plasma volume 3 to 4 times the volume infused whereas normal saline generally expanded plasma volume less than 30% of the volume infused (9). Thus, it appeared that HSD could be as effective as isotonic solution for resuscitation, but at 1/10 or 1/12 the volume. The following review summarizes the experience over the past decade with HSD, in its proposed use to treat hemorrhagic hypotension, as well as other related conditions. Emphasis is placed on the effectiveness of HSD to achieve the physiological goals of fluid resuscitation therapy.

PHYSIOLOGICAL GOALS OF FLUID RESUSCITATION

The primary goal of any fluid resuscitation regimen in the treatment of hemorrhagic hypotension is to improve survival rates. In an attempt to improve survial, treatment strives for three major therapeutic effects: 1) achieve hemodynamic stability, 2) correct metabolic disturbances and 3) return tissue perfusion to normal. It is believed that fluid resuscitation can achieve these beneficial effects by restoring plasma volume and restoring adequate blood flow to vital organs, thereby preventing insults arising from ischemia secondary to the trauma event. The present review addresses these goals in our evaluation of the efficacy of HSD.

Survival

A number of experimental animal species and models of hemorrhage have been employed to investigate the potential efficacy of small volume resuscitation with HSD to improve survival. In an early study using a potentially lethal hemorrhage model in pigs, HSD at a dose of 11.5 ml/kg (25% of the shed blood volume) markedly improved survival (14). Maningas, et al. (14) observed 100% survival in pigs infused with HSD, whereas survival in animals infused with normal saline (NS) was 13%. Infusion of the individual components of HSD, 7.5% NaCl (HS) or 6% Dextran-70 (D-70), resulted in survival rates of 53% and 69%, respectively. Encouraged by these results, a subsequent survival study found that significantly higher survival rates than those observed with NS were achieved with HSD infusions between 4 and 11.5 ml/kg (15,16). In a severe fixed-pressure hemorrhage model in dogs, survival was also higher following infusion of 6 ml/kg HSD than after infusion of its individual components, HS or D-70 (17). Also, Chudnofsky, et al. (18) observed significantly higher survival rates in a continuous hemorrhage swine model following slow infusion of HSD in comparison with infusion of NS.

Although considered a more relevant model of accidental, criminal, or military trauma, the ability of HSD to resuscitate from uncontrolled bleeding has not received much attention. Basically, the concept of

giving a large volume of fluid when bleeding has not been controlled is counter to general rules of first aid. Nevertheless, concerns have arisen that under circumstances of uncontrolled bleeding, administration of HSD could lead to increased bleeding.

In a recently established aortotomy model in anesthetized swine (19), infusion of RL at 3 times the blood volume lost resulted in increased bleeding and higher mortality compared with unresuscitated animals (20). Immediate infusion of HSD in this animal model also resulted in greater bleeding and higher mortality compared with untreated controls, but the magnitude was less than in the RL group (40% vs. 0% survival) (21). It was later shown that delaying the HSD infusion or administering it by slow infusion reduced mortality to near control levels (Bruttig, et al., unpublished results). Generally, these data agree with those observed following administration of HS or HSD in an uncontrolled hemorrhage model in rats (22,23), although the relevance of this tail resection model to human hemorrhagic shock has been questioned (24,25). It should be noted however, that slow infusion of HSD during the period of hemorrhage did not adversely affect survival in a swine model (18).

Interestingly, a pressure driven hemorrhage model has been developed in dogs to mimic uncontrolled hemorrhage (26). Although HSD infusion in this study led to greater cumulative blood loss, its administration also lengthened survival. The greatest hemodynamic and metabolic improvement was derived from 2 doses of HSD together with LR infusion.

Survival was also the main criterion selected in the USA multicenter clinical trial to evaluate the efficacy and safety of HSD (27). This trial enrolled 422 trauma patients transported by ambulances to the Emergency Departments of 3 urban medical centers. Subjects were infused with 250 ml of HSD or RL followed by RL. Although overall 24 hr survival rates were not significantly different between the 2 groups, survival was significantly higher in those patients who required surgery (79% vs. 91%). In their initial helicopter transport study with 20 patients, Holcroft, et al. (28) reported overall improved survival in the HSD group

compared with the RL group. However, in their larger study of 83 patients, overall survival was not significantly different between the HSD and RL groups (25). Most recently, Younes, et al. (29) reported that 24 hr survival rates were significantly higher in HSD-infused patients with severe trauma compared with patients infused with NS. In addition, Vassar, et al. (30) reported that in their ambulance transport study, HS and HSD both improved upon the overall predicted survival rate in high risk trauma patients.

Analysis of these limited studies can only further stress the conclusions drawn by Holcroft, et al. (31,32) and Vassar, et al. (33) that in hospital setting trials with short transport times, the ability to gain venous access and to administer large amounts of fluids at rapid rates would make the detection of beneficial effects of HSD (i.e., improved survival) over and above conventional therapy extremely difficult. In addition, detection of improved survival following HSD administration can also be attenuated by the design of recent clinical trials in which HSD infusion has been followed by continuous infusion of large volumes of RL. The conclusion is that HSD would have the most benefit in prehospital use where infusion of large volumes of fluid is not possible. HSD was also successfully used in the operating room and emergency department, but its use was not advocated in the intensive care unit (32).

Hemodynamic Stability

Studies reporting the marked ability of HSD to improve survival in potentially lethal models of controlled hemorrhage in experimental animals were often accompanied by physiological and biochemical evaluations to better understand the mechanisms involved. Since an overall improvement in survival in clinical studies with HSD has not been clearly defined, these physiological and biochemical variables have been measured to evaluate the potential efficacy of HSD. In their early evaluation of the effects of HSD in pigs, Maningas, et al. (14) reported that HSD also corrected the drop in blood pressure associated with hemorrhage.

A number of subsequent studies in conscious swine employed a fixed-volume hemorrhage model to investigate the potential efficacy of a single bolus of 4 ml/kg HSD for up to 4 hr following hemorrhage. Based on the survival data discussed above (14,15), this dose was chosen to circumvent the potential hypernatremia and its associated neurological sequelae (15). Wade, et al. (16) showed improved hemodynamics following HSD infusion compared with either HS or NS infusion. Importantly, these studies indicated that HSD could restore cardiac output to prehemorrhage levels without a major increase in blood pressure (16). In addition, studies by Dubick, et al. (34) and Sondeen, et al. (35) observed that HSD improved renal function and urinary output; factors greatly diminished by hemorrhage.

Other studies in dogs, swine and rabbits were designed to evaluate the efficacy of HSD under a simulated prehospital scenario that included time for ambulance request and dispatch, travel to the scene, patient evaluation and setting up the IV (18,34,36-38). In many cases this involved up to a 30 min delay before resuscitating from hypovolemia and monitoring the animal for at least 2 hr without additional fluid administration. In their continuous hemorrhage model in swine, Chudnofsky, et al. (18) observed significantly improved hemodynamics as denoted by increased mean arterial pressure (MAP), cardiac index, and reduced systemic vascular resistance following HSD infusion. Similar observations were reported by Siritongtaworn, et al. (36) in a hemorrhagic shock model in dogs.

In addition, Kramer, et al. (37) reported that in a hemorrhaged sheep model, HSD was effective in rapidly restoring blood pressure and cardiac output and improving urine output whereas the same dose of RL was ineffective. The study also demonstrated that when additional RL was given 30 min after the initial infusions in both groups, the total fluid requirements for full restoration of cardiovascular function were significantly lower in the HSD than RL group. Further studies demonstrated that HSD was equally effective when infused peripherally and centrally, and its hypertonicity did not damage peripheral vessels (39).

Further evaluation of these experimental studies suggested that improved hemodynamic stability was attributable to the ability of HSD to restore blood volume. Hands, et al. (39) found that HSD restored plasma volume to prehemorrhage levels. In general, HSD expanded plasma volume approximately 3 to 4 times the infused volume in experimental animals (9). This expansion was greater and sustained significantly longer than following HS infusion (17). Kramer, et al. (40) also found that improved arterial pressure, improved cardiac output and plasma volume expansion occurred immediately after infusion of HSD.

Further evaluation of dextran metabolism following HSD infusion in both euvolemic and hemorrhaged rabbits and pigs revealed that the dextran was cleared from serum with a half-life of 7 hr in rabbits and 12 hr in pigs, (34,38); a sufficient time to satisfy its usefulness as a plasma volume expander for prehospital use. Importantly, hemorrhage did not significantly affect dextran half-life in these animal models. Also, the species difference in half-life suggested that dextran metabolism was related to metabolic body size (i.e., metabolic rate) supporting previous reports that dextrans are completely metabolized to CO_2 and water (11).

Improved hemodynamics have been observed in all clinical trials to date. In an initial field trial of trauma patients transported by helicopter to the University of California Davis Medical Center, Holcroft, et al. (28) reported a significant improvement in blood pressure, significantly higher Revised Trauma Score, and lower Injury Severity Scores in 10 patients treated with 250 ml of 7.5% NaCl/4.2% Dextran-70 compared with 10 patients treated with RL. In a second, larger, helicopter transport study of 83 patients, those infused with HSD followed by conventional fluids required less fluid before hospitalization and had higher blood pressures upon arrival at the hospital (25). Significantly improved systolic blood pressure was also noted in the USA Multicenter trial (27).

In a recent study, Chavez-Negrete, et al. (41) used either HSD or RL to treat 49 emergency patients presenting with acute upper gastrointestinal hemorrhage and arterial hypotension. The HSD infusion was also followed by crystalloid infusion. They reported marked improvement in blood pressure, urine output, and lower mortality in the HSD than RL group. Significantly, 10 of the 26 patients receiving HSD were infused intraosseously (IO), with results indistinguishable from those patients infused IV. In an experimental study with pigs, Dubick, et al. (42) observed complete, rapid vascular entry of both sodium and dextran following IO infusion of HSD. In addition, plasma volume expansion and cardiovascular parameters measured were similar between pigs infused IO vs those infused IV. Also, Okrasinski, et al. (43) recently showed that HSD infused IO was effective in resuscitating dogs bled 50% of their blood volume. Taken together, these studies support the potential usefulness of HSD vascular delivery via the IO route as a viable alternative in emergency scenarios where vascular access is compromised.

Metabolic Effects

Numerous studies in experimental animals have shown that HSD infusion corrects the metabolic derangements associated with hemorrhage. Wade, et al. (44) and Hannon, et al. (45,46) have reported that HSD infusion reversed the hormonal abormalities, helped normalize the relationship between O_2 demand and O_2 delivery, and improved other metabolic disorders, such as deleterious blood gas and acid-base disturbances, associated with hemorrhage in swine. These observations have also been seen in dogs and sheep (17,47). In their controlled hemorrhage model, Becker, et al. (48) observed that 1 hr after 4 ml/kg HSD infusion, O_2 delivery, hepatic blood flow, and hepatic ATP production were improved as effectively as full RL resuscitation.

Initial reports from human trials with HSD have confirmed the results from animal studies. HSD infusion improved arterial O_2 tension with less total fluid required when compared with trauma patients

receiving RL (25). In the USA multicenter trial,
evidence for metabolic derangements associated with
trauma, (e.g., altered pH, bicarbonate concentrations,
blood gases, etc.) were equally corrected by HSD-RL or
RL infusions, when these values were determined upon
admission to the emergency room (27). In general, the
normalization of PO_2 and other metabolic variables
following HSD infusion in trauma patients has been
attributed to the hemodynamic improvement associated
with its use.

Microcirculation

It is recognized that effective resuscitation from
hemorrhagic hypotension must improve blood flow and
restore proper tissue and organ perfusion. In an early
study in swine, Maningas (49) showed that an 11.5 ml/kg
dose of HSD improved blood flow to the myocardium,
kidneys, liver, small intestine, and pancreas. He
concluded that this improved regional blood flow could
help explain the improved survival in HSD-resuscitated
pigs and that this improved flow could attenuate later
complications associated with hemorrhagic shock. In
addition, investigations in rabbits, dogs, and rats
have evaluated the ability of 4 ml/kg HSD to improve
tissue perfusion following hemorrhage, as a potential
mechanism to explain its ability to improve survival
and reduce the metabolic consequences of hemorrhagic
shock. In general, HSD was very effective as a small
volume resuscitation solution to improve mesenteric and
renal microcirculation (50-53). HSD improved capillary
flow and reversed capillary narrowing following
hemorrhage (53). Mazzoni, et al. (54) noted that small
volume infusion of HSD restored rabbit muscle capillary
diameter to prehemorrhage values by 30 min after
infusion, whereas HS, Macrodex (6% D-70), or RL were
not as effective. In addition, HSD was more effective
than RL in restoring skeletal muscle blood flow and
"intrinsic" microvascular reactivity in a rabbit
uncontrolled hemorrhage model, suggesting that HSD
administration can result in more effective total
resuscitation from massive hemorrhage than conventional
therapy (55). This speculation is consistent with the
conclusions of Mazzoni, et al. (54) that the ability of
HSD to osmotically shrink swollen endothelium and

reinstate capillary flow has important clinical implications in treating hemorrhagic shock or other low flow (ischemic) states.

OTHER USES OF HSD
Endotoxic Shock

Only a few investigations have explored other potential clinical uses of HSD. In a dog model of endotoxin shock, a bolus of 4 ml/kg HSD followed by RL infusion was more effective than RL alone in improving blood pressure and cardiac output and in correcting acid-base disturbances induced by the endotoxin shock (56). In addition, the total volume requirements for resuscitation and net fluid gain were about 3 and 5 times greater, respectively, in the RL than HSD group.

Head Trauma

The potential benefits of HSD in head trauma were further investigated in a porcine model of combined hemorrhagic shock and focal cryogenic brain injury (57). A bolus of 4 ml/kg HSD followed by infusions of either RL or hypertonic sodium lactate effectively improved hemodynamics associated with hemorrhage and improved cerebral blood flow with lower intracranial pressure better than RL treatment alone. Since the improved function induced by hypertonic resuscitation persisted for up to 3 hr, the authors concluded that such treatment could buy time for surgical interventions that might prevent or reduce secondary brain injury.

Intraoperative hypovolemia

Pascual, et al. (58) recently used a porcine model to investigate the efficacy of continuous infusion of HSD for the treatment of intraoperative hypovolemia. HSD infusion was regulated to maintain aortic blood flow at baseline levels. Since hypovolemic hypotension can occur during extensive surgical procedures, particularly in patients who have incurred multiple trauma, it is recognized that conventional fluid therapy can lead to volume overload and its associated

abnormalities in plasma electrolytes, metabolic disturbances, coagulopathies, etc. The study demonstrated that HSD reduced overall fluid requirements and maintained hemodynamics and pulmonary function. Currently, hypertonic solutions are being investigated experimentally to reduce overall fluid volume requirements associated with cardio-pulmonary bypass operations (Kramer, personal communication).

Burns

HSD has also been investigated to determine its effects on microvascular permeability in a canine hind paw burn model (59). Using hypertonic solutions in treating burns has been proposed as a means to reduce overall fluid requirements and to reduce edema. Under the conditions of this study, Dextran-70 alone was effective in reducing edema formation, but this benefit was eliminated in the presence of HS. In a burn model in sheep, infusion of 4 ml/kg HSD produced a short-lived (60 min) plasma volume expansion, whereas NS did not expand plasma volume (60). Considered together, these limited studies indicate that HSD would be less effective under conditions associated with capillary damage, as in burns.

Hypotension

HSD has recently been investigated as a potential treatment for hypotension in a randomized, blinded, crossover clinical trial in 9 patients with renal dialysis-induced hypotension (61). HSD raised blood pressure and tended to lower the incidence of hypotension with no overt signs of side effects.

ADVERSE EFFECTS

Since the concept was introduced to use HSD in the prehospital or field resuscitation from hypovolemic hypotension, its use has met resistance from some individuals in the medical/surgical community. This resistance is an apparent extension of long-publicized side effects associated with early formulations of

dextran solutions. These cited side effects include the potential for difficulties in typing and cross matching blood, increased bleeding, anaphylactoid reactions, and impaired renal function. The addition of hypertonic saline to dextran raised concerns of hypernatremia and its associated convulsions and hyperchloremic acidosis. Also, HSD could be detrimental when used in dehydrated or heat-stressed patients.

Extensive toxicological testing of HSD was done to support the New Drug Application for HSD submitted to the FDA. Irritation studies in rabbits (62), mice (63), and sheep (39) found HSD to be no more irritating following IV infusion than RL. In addition, both acute and subacute toxicity studies evaluated the effects of HSD and its individual components, HS and D-70, following either a single infusion or daily infusions for 14 days at the maximum tolerated dose (MTD) (64-67). Preliminary studies found the MTD to be 20 ml/kg in dogs and 16 ml/kg in rabbits; i.e., 4 to 5 times the proposed single therapeutic dose for humans.

In acute and subacute toxicity studies in dogs (64) the MTD of HSD did not significantly affect serum IgG, IgM, or complement C3 concentrations, suggesting that the use of HSD would not be associated with widespread allergic complications. In both dogs and rabbits, such high doses of HSD induced mild transient behavioral effects and transient changes in serum aminotransferase or alkaline phosphatase concentrations (65-67). Creatine kinase activity in serum was not affected. As expected, these changes were more pronounced in animals receiving daily infusions at the MTD and were generally associated with the HS component of HSD. Even at such high doses, serum BUN or creatinine concentrations were not different from baseline values, suggesting that HSD did not adversely affect renal function (65-67). The few deaths that occurred in the rabbit studies (66,67) were generally attributable to volume overload. It should also be mentioned that at the therapeutic dose of 4 ml/kg, HSD infusion did not activate the kallikrein-kinin system (68).

In experimental animals, infusion of HSD at 4 ml/kg resulted in elevations up to 12 mEq/L in plasma Na concentrations (16,37). Although in some experiments plasma Na exceeded 160 mEq/L, these levels were transient and were not associated with overt behavioral effects (37). HSD infusion in hemorrhaged swine also produced an immediate increase in plasma Cl concentrations (69) which was associated with a 0.04 drop in plasma pH and increased base deficit (69). Nevertheless, HSD infusion improved acid-base status more effectively than isotonic resuscitation (46,69).

As expected, upon admittance to the emergency room trauma patients receiving HSD-RL presented with elevated plasma Na and Cl concentrations and higher osmolalities than RL-infused patients (25,27,28,31,33). Blood pH, however, has not been significantly different in these patients in any clinical study. These variables were essentially normalized by 24 hr following admission to the hospital (27). In no case have elevated plasma Na concentrations nor osmolality-induced neurological disturbance been observed (25,27,28,33).

The effects of HSD on typing and cross-matching of blood was investigated with human blood in vitro (70). At a 1:5 mixture of HSD to blood, the highest concentration perceived to occur in a hemorrhaged patient who survives to treatment, no effect on ABO, Rh and MN typing was observed in either fresh or 35-day stored blood. In addition, HSD produced no significant lysis with fresh cells and a minimum level in stored blood. HSD also did not alter the metabolic activity of the red blood cells.

This 1:5 ratio for HSD to human blood in vitro resulted in a slight prolongation of prothrombin (PT), but not the activated partial thromboplastin (APTT) time, when compared with these variables in blood diluted with NS (71). This high dose of HSD also decreased human platelet aggregation, which was not affected at a 1:10 ratio of HSD to platelet-rich plasma (71). It was subsequently determined that both these effects were attributable to the HS component of HSD. Considering the rapid redistribution of sodium

following IV infusion of HSD (16), these data suggested that the use of HSD at 4 ml/kg would induce little clinical hemostatic impairment. To test this further, PT and APTT were evaluated in rabbits (72) and PT, APTT, platelet aggregation and bleeding times were evaluated in pigs (73) infused with HSD. In both studies no significant changes were observed in PT or APTT over a 7 day experimental period (72,73). In addition, HSD infusion in pigs did not significantly affect platelet aggregation that was determined over the first 24 hr, and bleeding times were not prolonged at 1 hr and 2 hr after HSD infusion (73).

The few human trials with HSD also addressed possibly adverse effects associated with its use. In the large USA Multicenter trial, no anaphylactoid nor dextran-induced coagulopathies were observed (27). Although the data were not significantly different, a lower incidence of complications, such as ARDS, renal failure, and coagulopathies, was observed in the HSD group. In prospective, double blind emergency department trials, no difficulty with cross matching of blood nor increased bleeding were observed (31,33). In addition, PT or APTT measurements have been normal (27). No anaphylactoid reactions occurred and there were no cases of central pontine myelinolysis (33). Also, hypernatremia or hyperosmolality associated with HSD infusion appeared to be clinically insignificant due to other factors associated with the traumatic injury (33).

As a plasma volume expander, HSD draws water from the cellular and extracellular space into the vascular compartment. Consequently, concerns arose that use of HSD in dehydrated patients could be detrimental. This question was recently addressed by Wade, et al. (74) in a short-term (3 hr) study in moderately dehydrated, hemorrhaged pigs. This dehydration-hemorrhage model is potentially 100% lethal if untreated. Under these conditions, HSD infusion significantly improved survival. Importantly, the hemodynamic effects of HSD in resuscitating from hemorrhage were not compromised by dehydration (74). In a long-term (7 d) study in moderately dehydrated, hemorrhaged sheep, Sondeen, et al. (75) did not observe any adverse neurological or

behavioral effects, and plasma Na concentrations or osmolality were not raised to exceedingly high concentrations following HSD infusion. Additional studies in this animal model did not detect any adverse effects on renal function (Sondeen, et al. unpublished observations) and HSD infusion was equally effective in resuscitating these animals from hemorrhage compared with euhydrated sheep (76).

This concern of dehydration was also extended to possible situations of combined dehydration and hyperthermia, as might be encountered in trauma patients recovered from a desert climate such as that encountered by the Allied Military in the recent Desert Shield/Storm Operation. In preliminary studies with dehydrated, hyperthermic rats, HSD was more beneficial than saline for the treatment of heat stroke, regardless of the animal's hydration status (77).

In animal studies assessing the potential toxicity associated with HSD infusion at the proposed therapeutic dose of 4 ml/kg, no overt toxicity was detected. The small amount of dextran infused also did not affect coagulation, result in tissue and blood vessel damage, or induce allergic reactions. These observations have also been confirmed in the limited human trials conducted to date. Also, it does not appear that HSD infusion would be detrimental in hyperthermia or dehydration.

CONCLUDING REMARKS

The data from animal studies suggest that HSD is an effective plasma volume expander in small volumes. By virtue of its use as a small volume resuscitation solution, RL would be totally ineffective at the same dose. It has been amply demonstrated in a variety of different hemorrhage models and animal species that HSD improves hemodynamics and microcirculatory tissue perfusion and corrects metabolite abnormalities. In addition, HSD infusion improves survival in animal models of controlled hemorrhage. The only experimental situation in which the efficacy of HSD, as well as other potential resuscitation solutions, is not as

clearly defined is uncontrolled hemorrhage. Determining the role of HSD in uncontrolled hemorrhage may only be a matter of delaying or controlling its rate of infusion. Although rapid administration of HSD in clear instances of uncontrolled bleeding appears to be contrary to accepted dogma of first aid, its proper use may prolong survival despite increased bleeding. This may be particularly relevant in the military setting where delays may be encountered in the evacuation of the injured soldier to medical treatment facilities. Improper use of HSD under circumstances of uncontrolled bleeding may only accelerate unavoidable death. It should also be noted that recent studies with HSD formulations containing 12% or 24% dextran have shown slightly better resuscitation than with HSD containing 6% dextran (47,78). Further studies are required to better evaluate the most efficacious hypertonic saline dextran formulation and to define its most appropriate mode of use.

As the function of HSD is defined by the cellular physics of its individual components, HS and D-70, HSD should be equally effective in humans. As expected, traumatic injury in humans is varied and more complicated than animal hemorrhage models. Consequently, the efficacy of HSD has not been clearly established in clinical trials. To date, a single bolus of 250 ml of HSD infused in the field and followed by infusion of RL appears of benefit in hypotensive trauma victims requiring surgery or with head injury. Further human trials with HSD are required to best define the patient population that would benefit most from the prehospital administration of HSD. In addition, HSD can be as effective when infused IO as IV. It is also important to note that from the results of extensive toxicological testing in experimental animals and from the lack of adverse effects observed in the human field trials at the proposed therapeutic dose of 4 ml/kg, minimal adverse effects should be anticipated. Therefore, HSD should be a drug with a high safety factor and a large benefit-to-risk ratio. Further studies are necessary to refine the optimal dextran concentration in HSD or its dose, as well as to define additional clinical applications.

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